

# The analysis of stochastic stability of stochastic models that describe tumor-immune systems

O. Chiş<sup>1</sup>, A. Sandru<sup>2</sup>, D. Opris<sup>3</sup>

<sup>1</sup> Euro University "Drăgan", Lugoj, Romania,  
email: chisoana@yahoo.com

<sup>2</sup> Faculty of Exact Sciences, Aurel Vlaicu University, Arad, Romania,  
email: sandruandrea@gmail.com

<sup>3</sup> Faculty of Mathematics and Informatics, West University of  
Timișoara, Romania,  
email: opris@math.uvt.ro

**Abstract:** In this paper we investigate some stochastic models for tumor-immune systems. To describe these models, we used a Wiener process, as the noise has a stabilization effect. Their dynamics are studied in terms of stochastic stability in the equilibrium points, by constructing the Lyapunov exponent, depending on the parameters that describe the model. Stochastic stability was also proved by constructing a Lyapunov function. We have studied and analyzed a Kuznetsov-Taylor like stochastic model and a Bell stochastic model for tumor-immune systems. These stochastic models are studied from stability point of view and they were represented using the second Euler scheme and Maple 12 software.

## 1 Introduction

Stochastic modeling plays an important role in many branches of science. In many practical situations perturbations appear and these are expressed using white noise, modeled by Brownian motion. We will study stochastic dynamical systems that are used in medicine, in describing a tumor behavior, but still we don't know much about the mechanism of destruction and establishment of a cancer tumor, because a patient

may experience tumor regression and later a relapse can occur. The need to address not only preventative measures, but also more successful treatment strategies is clear. Efforts along these lines are now being investigated through immunotherapy ([6], [21], [23]).

This tumor-immune study, from theoretical point of view, has been done for two cell populations: effector cells and tumor cells. It was predicted a threshold above which there is uncontrollable tumor growth, and below which the disease is attenuated with periodic exacerbations occurring every 3-4 months. There was also shown that the model does have stable spirals, but the Dulac-Bendixson criterion demonstrates that there are no stable closed orbits. It is consider ODE's for the populations of immune and tumor cells and it is shown that survival increases if the immune system is stimulated, but in some cases an increase in effector cells increases the chance of tumor survival.

In the last years, stochastic growth models for cancer cells were developed, we mention the papers of W.Y. Tan and C.W. Chen [20], N. Komarova, G. Albano and V.Giorno [2], L. Ferrante, S. Bompadre, L. Possati and L. Leone [7], A. Boondirek Y. Lenbury, J. Wong-Ekkabut, W. Triampo, I.M. Tang, P. Picha [4].

Our goal in this paper is to construct stochastic models and to analyze their behavior around the equilibrium point. In these points stability is studied by analyzing the Lyapunov exponent, depending of the parameters of the models. Numerical simulations are done using a deterministic algorithm with an ergodic invariant measure. In this paper the authors studied and analyzed two stochastic models. In Section 2, we considered a Kuznetsov and Taylor stochastic model. Beginning from the classical one, we have studied the case of positive immune response. We gave the stochastic model and we analyzed it in the equilibrium points. Numerical simulations for this new model are presented in Section 2.1. In Section 3 we presented a general family of tumor-immune stochastic systems and from this general representation we analyzed Bell model. We wrote this model as a stochastic model, using Annexe 1, and we discussed its behavior around the equilibrium points. We have proved stochastic stability around equilibrium point using two methods. The first one consists of expressing the Lyapunov exponent, and then drawing the conclusion when the considered system is stable. The second method is a way of constructing a Lyapunov function and determining sufficient conditions such that the system is stable. Numerical simulations were done using the software Maple 12 and we implemented the second order Euler scheme for a representation of the discussed stochastic models.

## 2 Kuznetsov and Taylor stochastic model

The study of tumor-immune interaction is determined by the behavior of two populations of cells: effector cells and tumor cells. We will construct the stochastic models using well known deterministic models and we analyze stochastic stability around the equilibrium points. The analysis is done using Lyapunov exponent method.

We will begin our study from the deterministic model of Kuznetsov and Taylor [14]. This model describes the response of effector cells to the growth of tumor cells and takes into consideration the penetration of tumor cells by effector cells, that causes the interaction of effector cells. This model can be represented in the following way:

$$\begin{cases} \dot{x}(t) = a_1 - a_2x(t) + a_3x(t)y(t), \\ \dot{y}(t) = b_1y(t)(1 - b_2y(t)) - x(t)y(t), \end{cases} \quad (1)$$

where initial conditions are  $x(0) = x_0 > 0$ ,  $y(0) = y_0 > 0$  and  $a_3$  is the immune response to the appearance of the tumor cells.

In this paper we consider the case of  $a_3 > 0$ , that means that immune response is positive. For the equilibrium states  $P_1$  and  $P_2$ , we study the asymptotic behavior with respect to the parameter  $a_1$  in (1). For  $b_1a_2 < a_1$ , the system (1) has the equilibrium states  $P_1(x_1, y_1)$  and  $P_2(x_2, y_2)$ , with

$$x_1 = \frac{a_1}{a_2}, y_1 = 0, \quad (2)$$

$$x_2 = (b_1(a_3 - b_2a_2) + \sqrt{(\Delta)})/(2a_3), y_2 = (b_1(a_3 + b_2a_2) - \sqrt{(\Delta)})/(2b_1b_2a_3) \quad (3)$$

where  $\Delta = b_1^2(b_2a_2 - a_3)^2 + 4b_1b_2a_1a_3$ .

We associate a stochastic system of differential equations to the ordinary system of differential equations (1).

In [14] it is shown that there is an  $a_{10}$ , such that if  $0 < a_1 < a_{10}$ , then the equilibrium state  $P_1$  is asymptotically stable, and for  $a_1 > a_{10}$  the equilibrium state  $P_1$  is unstable. If  $a_1 < a_{10}$ , then the equilibrium state  $P_2$  is unstable and for  $a_1 > a_{10}$  it is asymptotically stable.

Let us consider  $(\Omega, \mathcal{F}_{t \geq 0}, \mathcal{P})$  a filtered probability space and  $(W(t))_{t \geq 0}$  a standard Wiener process adapted to the filtration  $(\mathcal{F})_{t \geq 0}$ . Let  $\{X(t, \omega) = (x(t), y(t))\}_{t \geq 0}$  be a stochastic process.

The system of Itô equations associated to system (1) is given by

$$\begin{cases} x(t) = x_0 + \int_0^t (a_1 - a_2x(s) + a_3x(s)y(s))ds + \int_0^t g_1(x(s), y(s))dW(s), \\ y(t) = y_0 + \int_0^t ((b_1y(s)(1 - b_2y(s)) - x(s)y(s)))ds + \int_0^t g_2(x(s), y(s))dW(s), \end{cases} \quad (4)$$

where the first integral is a Riemann integral, and the second one is an Itô integral.  $\{W(t)\}_{t>0}$  is a Wiener process [17].

The functions  $g_1(x(t), y(t))$  and  $g_2(x(t), y(t))$  are given in the case when we are working in the equilibrium state. In  $P_1$  those functions have the following form

$$\begin{aligned} g_1(x(t), y(t)) &= b_{11}x(t) + b_{12}y(t) + c_{11}, \\ g_2(x(t), y(t)) &= b_{21}x(t) + b_{22}y(t) + c_{21}, \end{aligned} \tag{5}$$

where

$$c_{11} = -b_{11}x_1 - b_{12}y_1, \quad c_{21} = -b_{21}x_1 - b_{22}y_1. \tag{6}$$

In the equilibrium state  $P_2$ , the functions  $g_1(x(t), y(t))$  and  $g_2(x(t), y(t))$  are given by

$$\begin{aligned} g_1(x(t), y(t)) &= b_{11}x(t) + b_{12}y(t) + c_{12}, \\ g_2(x(t), y(t)) &= b_{21}x(t) + b_{22}y(t) + c_{22}, \end{aligned} \tag{7}$$

where

$$c_{12} = -b_{11}x_2 - b_{12}y_2, \quad c_{22} = -b_{21}x_2 - b_{22}y_2. \tag{8}$$

The functions  $g_1(x(t), y(t))$  and  $g_2(x(t), y(t))$  represent the volatilisations of the stochastic equations and they are the therapy test functions.

## 2.1 The analysis of SDE (4). Numerical simulation.

Using the formulae from Annexe 1, Annexe 2, and Maple 12 software, we get the following results, illustrated in the below figures. For numerical simulations we use the following values of parameters:

$$a_1 = 0.1181, \quad a_2 = 0.3747, \quad a_3 = 0.01184, \quad b_1 = 1.636, \quad b_2 = 0.002.$$

The matrices  $A$  and  $B$  are given, in the equilibrium point  $P_1(\frac{a_1}{a_2}, 0)$  by

$$A = \begin{pmatrix} -a_2 + a_3y_1 & a_3x_1 \\ -y_1 & b_1 - 2b_2y_1 - x_1 \end{pmatrix}, \quad B = \begin{pmatrix} 10 & -2 \\ 2 & 10 \end{pmatrix}.$$

In a similar way, matrices  $A$  and  $B$  are defined in the other equilibrium point

$$P_2\left(\frac{(-b_1(b_2a_2 - a_3) + \sqrt{\Delta})}{2a_3}, \frac{(b_1(b_2a_2 + a_3) - \sqrt{\Delta})}{2b_1b_2a_3}\right),$$

with  $\Delta = b_1^2(b_2a_2 - a_3)^2 + 4b_1b_2a_1a_3$ .

Using second order Euler scheme, for the ODE system (1) and SDE system (4), we get the following orbits presented in the figures above.

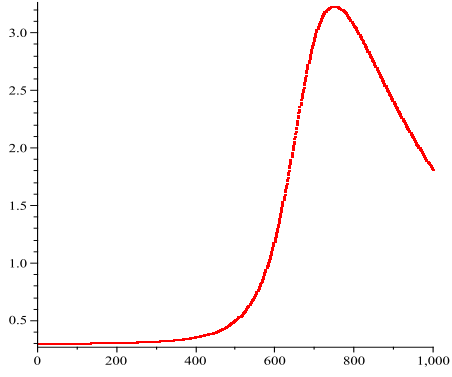


Figure 1:  $(n, x(n))$  in  $P_1$  for ODE (1)

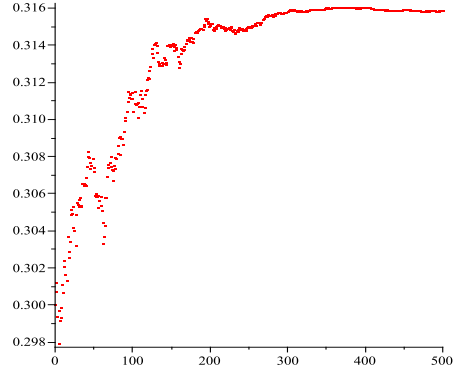


Figure 2:  $(n, x(n, \omega))$  in  $P_1$  for SDE (4)

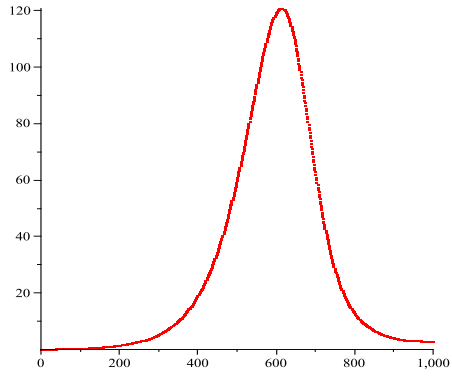


Figure 3:  $(n, y(n))$  in  $P_1$  for ODE (1)

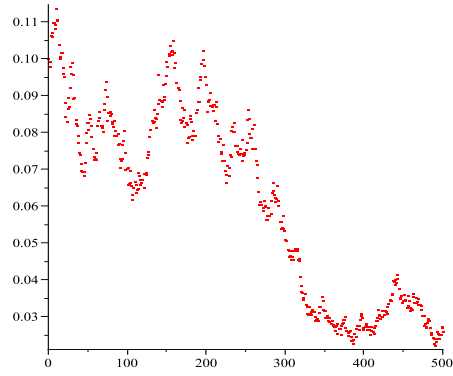


Figure 4:  $(n, y(n, \omega))$  in  $P_1$  for SDE (4)

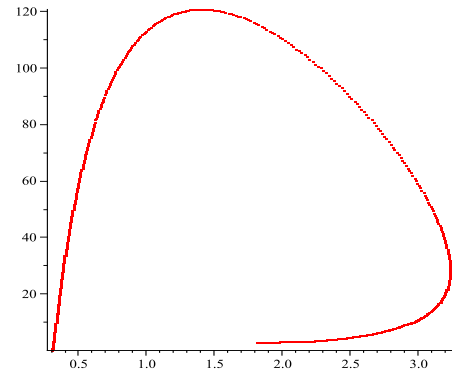


Figure 5:  $(x(n), y(n))$  in  $P_1$  for ODE (1)

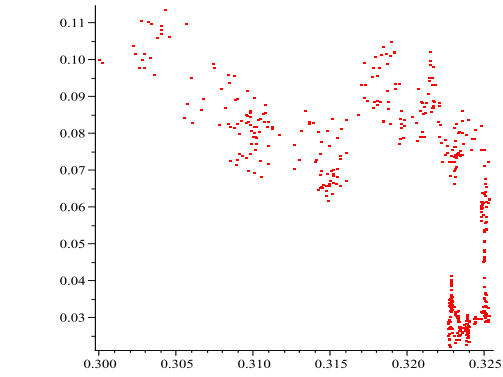


Figure 6:  $(x(n, \omega), y(n, \omega))$  in  $P_1$  for SDE (4)

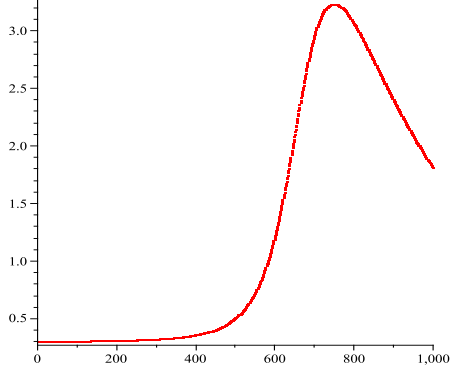


Figure 7:  $(n, x(n))$  in  $P_2$  for ODE (1)

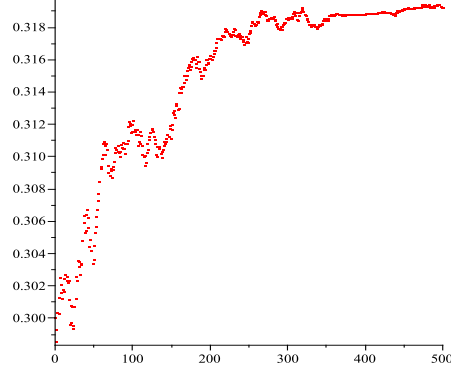


Figure 8:  $(n, x(n, \omega))$  in  $P_2$  for SDE (4)

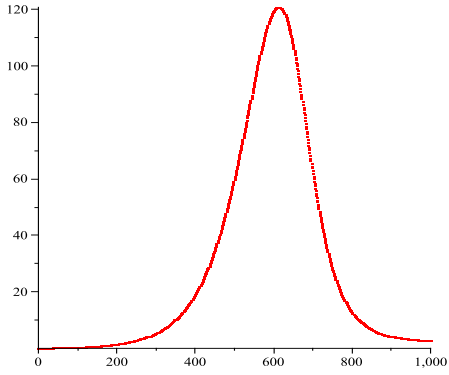


Figure 9:  $(n, y(n))$  in  $P_2$  for ODE (1)

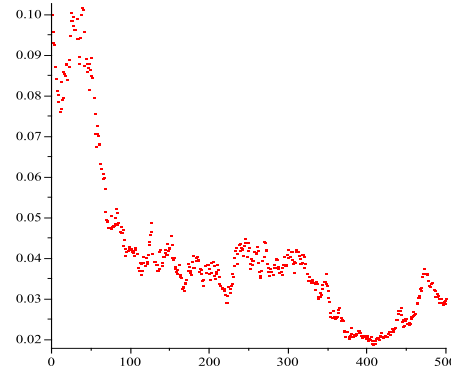


Figure 10:  $(n, y(n, \omega))$  in  $P_2$  for SDE (4)

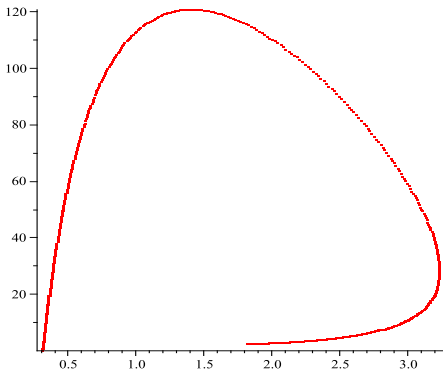


Figure 11:  $(x(n), y(n))$  in  $P_2$  for ODE (1)

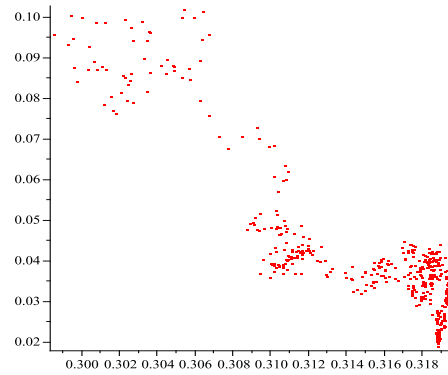


Figure 12:  $(x(n, \omega), y(n, \omega))$  in  $P_2$  for SDE (4)

The Lyapunov exponent variation, with the variable parameter  $b_{11} = \alpha$ , is given in Figure 13 for  $P_1$ , and in Figure 14 for the equilibrium point  $P_2$ .

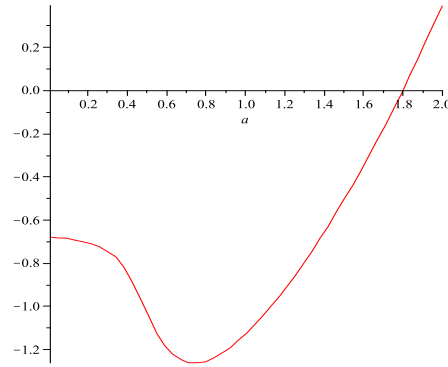
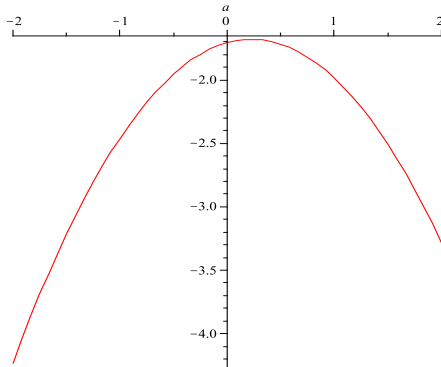


Figure 13:  $(\alpha, \lambda(\alpha))$  in  $P_1$  for ODE (1)    Figure 14:  $(\alpha, \lambda(\alpha))$  in  $P_2$  for SDE (4)

The Lyapunov exponent, for the equilibrium point  $P_1$  is negative, so  $P_1$  is asymptotically stable for each  $\alpha \in \mathbb{R}$ . For the second equilibrium point  $P_2$ , this point is asymptotically stable for all values when  $\lambda < 0$ , that means that  $P_2$  is unstable for all  $\alpha \in (-\infty, -1.8) \cup (1.8, \infty)$ .

### 3 A general family of tumor-immune stochastic systems

A Volterra-like model was proposed in [18] for the interaction between a population of tumor cells (whose number is denoted by  $x$ ) and a population of lymphocyte cells ( $y$ ) and it is given by

$$\begin{cases} \dot{x}(t) = ax(t) - bx(t)y(t), \\ \dot{y}(t) = dx(t)y(t) - fx(t) - ky(t) + u, \end{cases} \quad (9)$$

where the tumor cells are supposed to be in exponential growth (which is, however, a good approximation only for the initial phases of the growth) and the presence of tumor cells implies a decrease of the "input rate" of lymphocytes.

A general representation for such models can be considered in the form given by d'Onofrio in [6]:

$$\begin{cases} \dot{x}(t) = f_1(x(t), y(t)), \dot{y}(t) = f_2(x(t), y(t)), \\ x(0) = x_0, y(0) = y_0, \end{cases} \quad (10)$$

where  $x$  is the number of tumor cells,  $y$  the number of effector cells of immune system and

$$\begin{aligned} f_1(x, y) &= x(h_1x - h_2xy), \\ f_2(x, y) &= (h_3x - h_4x)y + h_5x. \end{aligned} \tag{11}$$

The functions  $h_1, h_2, h_3, h_4, h_5$  are given such that the system (10) admits the equilibrium point  $P_1(x_1, y_1)$ , with  $x_1 = 0$ ,  $y_1 > 0$ , and  $P_2(x_2, y_2)$ , with  $x_2 \neq 0$ ,  $y_2 > 0$ .

Deterministic models of this general form are the following

**Volterra model [22]** if  $h_1(x) = a_1$ ,  $h_2(x) = a_2x$ ,  $h_3(x) = b_3x$ ,  $h_4(x) = b_2$  and  $h_5(x) = -b_1x$ ;

**Bell model**  $h_1(x) = a_1x$ ,  $h_2(x) = a_2x$ ,  $h_3(x) = b_1x$ ,  $h_4(x) = b_3$  and  $h_5(x) = -b_2x + b_4$ ;

**Stepanova model [19]** with  $h_1(x) = a_1$ ,  $h_2(x) = 1$ ,  $h_3(x) = b_1x$ ,  $h_4(x) = b$  and  $h_5(x) = -b_2x + b_4$ ;

**Vladar-Gonzalez model [21]** if in (10) we consider  $h_1(x) = \log(K/x)$ ,  $h_2(x) = 1$ ,  $h_3(x) = b_1x$ ,  $h_4(x) = b_2 + b_3x^2$  and  $h_5(x) = 1$ ;

**Exponential model [23]** if in (10) we consider  $h_1(x) = 1$ ,  $h_2(x) = 1$ ,  $h_3(x) = b_1x$ ,  $h_4(x) = b_2 + b_3x^2$ , and  $h_5(x) = 1$ ;

**Logistic model [15]** if in (10) we consider  $h_1(x) = 1 - \frac{a_1}{x}$ ,  $h_2(x) = 1$ ,  $h_3(x) = b_1x$ ,  $h_4(x) = b_2 + b_3x^2$ , and  $h_5(x) = 1$ .

The analysis of these models was proven also using numerical simulations.

For a considered filtered probability space  $(\Omega, \mathcal{F}_{t \geq 0}, \mathcal{P})$  and a standard Wiener process  $(W(t))_{t \geq 0}$ , we consider the stochastic process in two dimensional space  $(\mathcal{F})_{t \geq 0}$ .

The system of Itô equations associated to system (10) is given, in the equilibrium point  $P(x_0, y_0)$ , by

$$\begin{cases} x(t) = x_0 + \int_0^t [x(s)(h_1(x(s)) - h_2(x(s))y(s))]ds + \int_0^t g_1(x(s), y(s))dW(s), \\ y(t) = y_0 + \int_0^t [(h_3(x(s)) - h_4(x(s)))y(s) + h_5(x(s))]ds + \int_0^t g_2(x(s), y(s))dW(s), \end{cases} \tag{12}$$

where the first integral is a Riemann integral, the second one is an Itô integral and  $\{W(t)\}_{t \geq 0}$  is a Wiener process [17].



The functions  $g_1(x, y)$  and  $g_2(x, y)$  are given in the case when we are working in the equilibrium state  $P_e$ , and they are given by

$$g_1(x, y) = b_{11}x + b_{12}y + c_{1e}, \quad (13)$$

$$g_2(x, y) = b_{21}x + b_{22}y + c_{2e},$$

where

$$c_{ie} = -b_{i1}x_e - b_{i2}y_e, \quad i = 1, 2, \quad (14)$$

and  $b_{ij} \in \mathbb{R}$ ,  $i, j = 1, 2$ .

### 3.1 Analysis of Bell model. Numerical simulations.

#### 3.1.1 Lyapunov exponent method

Following the algorithm for determining the Lyapunov exponent (Annexe 1) and the description of second order Euler scheme (Annexe 2) in Maple 12 software, we get the following results, illustrated in the figures below. For numerical simulations we use the following values of parameters:

$$a_1 = 2.5, a_2 = 1, b_1 = 1, b_2 = 0.4, b_3 = 0.95, b_4 = 2.$$

The matrices  $A$  and  $B$  are given, in the equilibrium point  $P_1\left(0, \frac{b_4}{b_3}\right)$  by

$$A = \begin{pmatrix} -a_2y_1 + a_1 & -a_2x_1 \\ -b_2 + b_1y_1 & b_1x_1 - b_3 \end{pmatrix}, \quad B = \begin{pmatrix} \alpha & -\beta \\ \beta & \alpha \end{pmatrix},$$

with  $\alpha = a \in \mathbb{R}$ ,  $\beta = -2$ . In a similar way the matrices  $A$  and  $B$  are defined in the other equilibrium point  $P_2\left(\frac{a_1b_3 - a_2b_4}{a_1b_1 - a_2b_2}, \frac{a_1}{a_2}\right)$ .

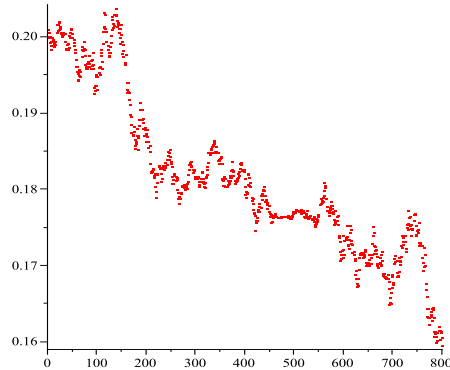
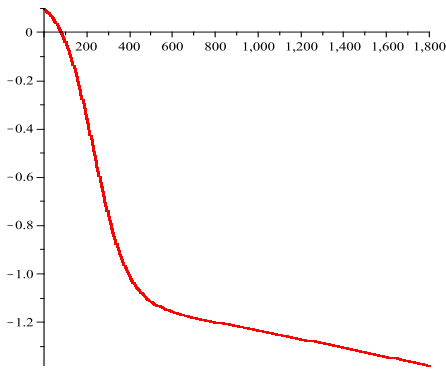


Figure 15:  $(n, x(n))$  in  $P_1$  for ODE (10)      Figure 16:  $(n, x(n, \omega))$  in  $P_1$  for SDE (12)

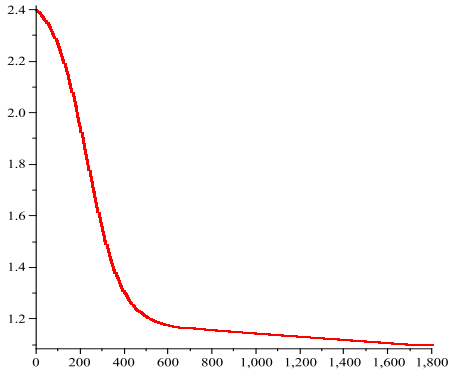


Figure 17:  $(n, y(n))$  in  $P_1$  for ODE (10)

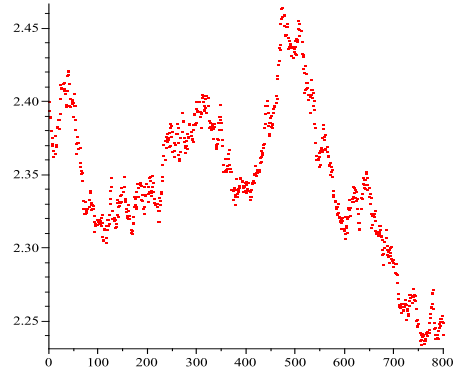


Figure 18:  $(n, y(n, \omega))$  in  $P_1$  for SDE (12)

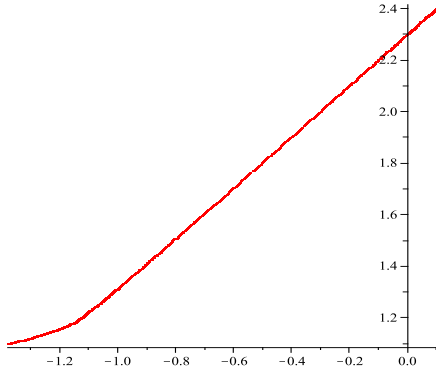


Figure 19:  $(x(n), y(n))$  in  $P_1$  for ODE (10)

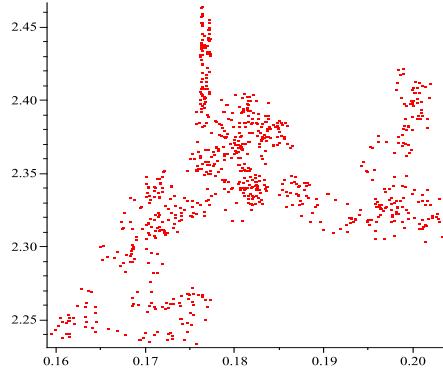


Figure 20:  $(x(n, \omega), y(n, \omega))$  in  $P_1$  for SDE (12)

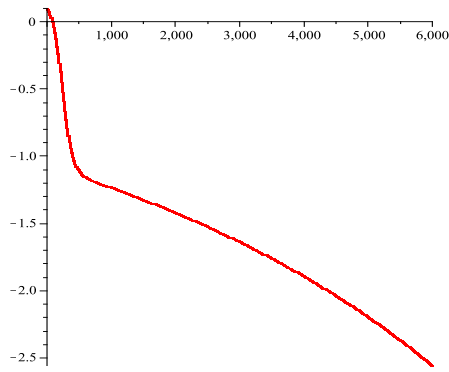


Figure 21:  $(n, x(n))$  in  $P_2$  for ODE (10)

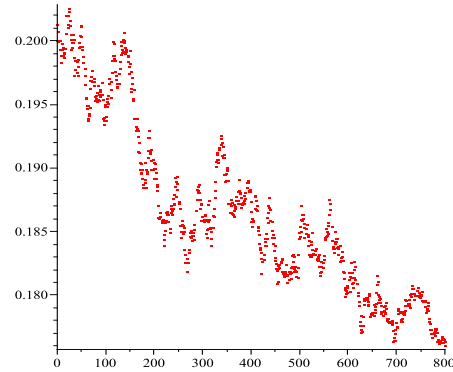


Figure 22:  $(n, x(n, \omega))$  in  $P_2$  for SDE (12)

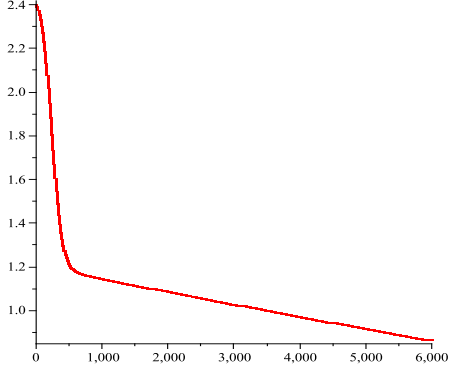


Figure 23:  $(n, y(n))$  in  $P_2$  for ODE (10)

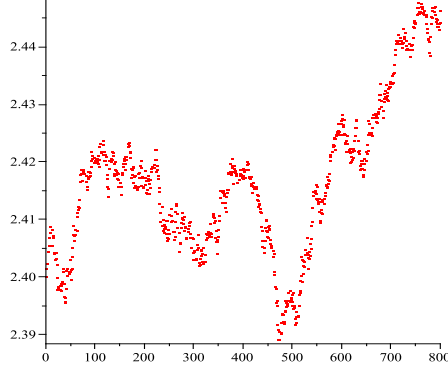


Figure 24:  $(n, y(n, \omega))$  in  $P_2$  for SDE (12)

The variation of Lyapunov exponent with the variable parameter  $b_{11} = \alpha$  is given in Figure 23 for  $P_1$  and in Figure 24 for  $P_2$ .

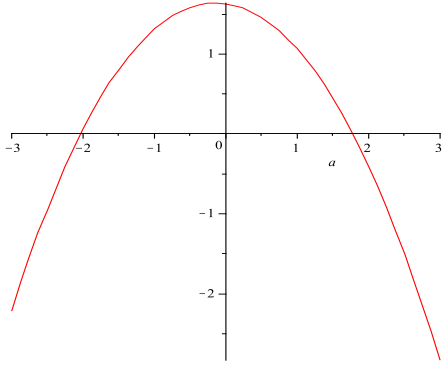


Figure 25:  $(\alpha, \lambda(\alpha))$  in  $P_1$  for ODE (10)

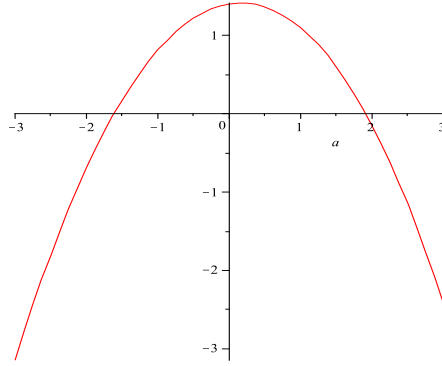


Figure 26:  $(\alpha, \lambda(\alpha))$  in  $P_2$  for SDE (12)

From the figures above, the equilibrium points  $P_1$  and  $P_2$  are asymptotically stable for all  $\alpha$  such that the Lyapunov exponents  $\lambda(\alpha) < 0$ , and unstable otherwise. So,  $P_1$  is asymptotically stable for  $\alpha \in (-\infty, -2.02) \cup (1.78, \infty)$  and  $P_2$  is asymptotically stable for  $\alpha \in (-\infty, -1.62) \cup (1.88, \infty)$ .

### 3.1.2 Lyapunov function method

For the system of differential equations that describes Bell model, the next assertions are true.

**Proposition 3.1 (a)** *The matrix of the system of differential equations that describes the linearized in  $P_2$  is*

$$A = \begin{pmatrix} 0 & a_{12} \\ a_{21} & a_{22} \end{pmatrix},$$

where

$$a_{12} = -\frac{a_2(a_1b_3 - a_2b_4)}{a_1b_1 - a_2b_2}, \quad a_{21} = \frac{a_1b_1 - a_2b_2}{a_2}, \quad a_{22} = -\frac{a_2(b_1b_4 + b_2b_3)}{a_1b_1 - a_2b_2};$$

(b) If  $a_1b_1 - a_2b_2 > 0$  and  $a_1b_3 - a_2b_4 > 0$ , then the equilibrium point  $P_2$  is asymptotically stable.

□

The stochastic model is given using a perturbation around the equilibrium point  $P_2(x_2, y_2)$ , in the following way

$$\begin{cases} dx(t) = x(t)(a_1 - a_2y(t))dt + \sigma_1(x(t) - x_{P_2})dW^1, \\ dy(t) = [(b_1x(t) - b_3)y(t) - b_2x(t) + b_4]dt + \sigma_2(y(t) - y_{P_2})dW^2, \end{cases} \quad (15)$$

with  $\sigma_1 > 0$ ,  $\sigma_2 > 0$ .

The linearized of system (15) in  $(0, 0)$  is given by

$$du(t) = h(u(t))dt + l(u(t))dW(t), \quad (16)$$

where  $u(t) = (u_1(t), u_2(t))^T$ ,  $W(t) = (W^1(t), W^2(t))^T$  and

$$h(u(t)) = \begin{pmatrix} (a_1 - a_2y_2)u_1(t) - x_2a_2u_2(t) \\ (b_1y_2 - b_2)u_1(t) + (b_1x_2 - b_3)u_2(t) \end{pmatrix}, \quad (17)$$

$$l(u(t)) = \begin{pmatrix} \sigma_1u_1(t) & 0 \\ 0 & \sigma_2u_2(t) \end{pmatrix}. \quad (18)$$

We consider the set  $D = \{(t \geq 0) \times \mathbb{R}^2\}$  and  $V : D \rightarrow \mathbb{R}$  a function of class  $C^1$  with respect to  $t$ , and of class  $C^2$  with respect to the other variables. We study the  $p$ -exponential stability of the solution  $(0, 0)$  of the linearized stochastic system (16). Using Theorem 4.4, from Anexe A1, for the function  $V : D \rightarrow \mathbb{R}$ ,

$$V(t, u) = \frac{1}{2}(\omega_1u_1^2 + \omega_2u_2^2), \quad \omega_1, \omega_2 \in \mathbb{R}_+, \quad (19)$$

we get the following result.

**Proposition 3.2** *If the following relations take place*

$$q_1 = \omega_1(a_2y_2 - a_1 - \sigma_1^2) > 0, \quad q_2 = \omega_2(b_3 - b_1y_2 - \sigma_2^2) > 0,$$

$$b_1 y_2 - b_2 > 0, \omega_1 = \frac{(b_1 y_2 - b_2)}{a_2 y_2} \omega_2,$$

then

$$dV(t, u) = -u(t)^T Q u(t),$$

with  $Q$  given by  $Q = \begin{pmatrix} q_1 & 0 \\ 0 & q_2 \end{pmatrix}$ .

The equilibrium point of (15) is asymptotically stable in quadratic square ( $p = 2$ ).

**Proof:** From (17), (18) and (19), we get

$$\begin{aligned} dV(t, u) &= \begin{pmatrix} (a_1 - a_2 y_2)u_1(t) - x_2 a_2 u_2 \\ (b_1 y_2 - b_2)u_1 + (b_1 x_2 - b_3)u_2 \end{pmatrix}^T \begin{pmatrix} \omega_1 u_1 \\ \omega_2 u_2 \end{pmatrix} + \begin{pmatrix} \sigma_1^2 \omega_1 u_1^2 & 0 \\ 0 & \sigma_2^2 \omega_2 u_2^2 \end{pmatrix} \\ &= -q_1 u_1^2 - q_2 u_2^2 + (\omega_2 (b_1 y_2 - b_2) - \omega_1 x_2 a_2) u_1 u_2. \end{aligned}$$

If the relations from the proposition take place, then we get

$$dV(t, u) = -u(t)^T Q u(t).$$

The matrix  $Q$  is symmetric and positive defined and has positive eigenvalues  $r_1 = q_1$  and  $r_2 = q_2$ . Let  $q_m$  be  $q_m = \min\{q_1, q_2\}$ . Results that

$$LV(t, u) \leq -q_m \|u(t)\|^2.$$

and so the equilibrium point is asymptotically stable in square mean.  $\square$

Let us choose the same parameters values for  $a_1, a_2, b_1, b_2, b_3$  as on the simulation of Lyapunov exponents. We use Maple 12 software for the implementation of the second order Euler method. We observe from the following graphics that the solution trajectories represent the stable characteristic, which validate our theoretical discussion for the system of differential equation (15), for the equilibrium point  $P_2$ .

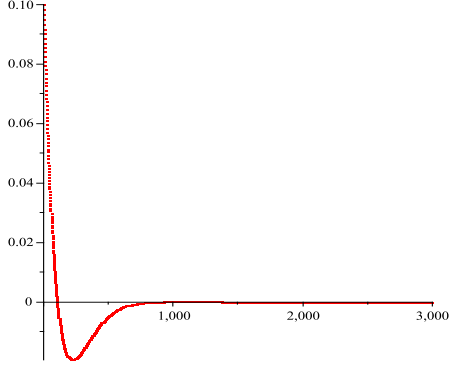


Figure 27:  $(n, x(n))$  in  $P_1$  for ODE (10)

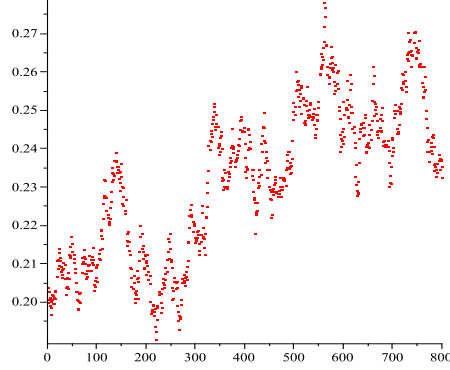


Figure 28:  $(n, x(n, \omega))$  in  $P_1$  for SDE (16)

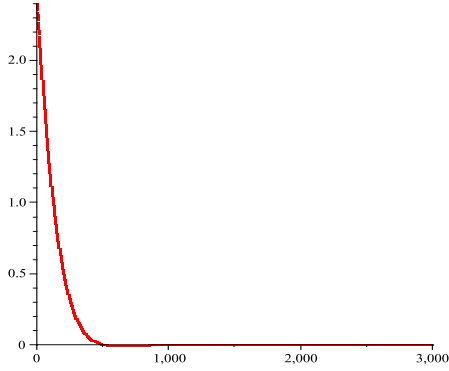


Figure 29:  $(n, x(n))$  in  $P_1$  for ODE (10)

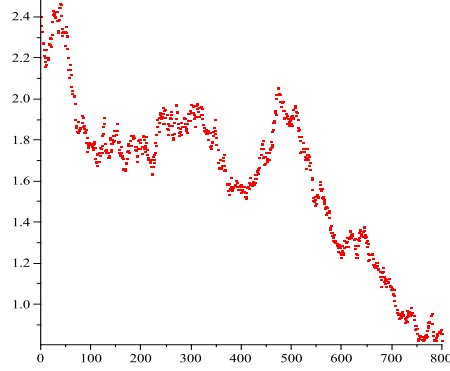


Figure 30:  $(n, x(n, \omega))$  in  $P_1$  for SDE (16)

## 4 Conclusions

In this paper we focused on two important tumor-immune systems, presented from stochastic point of view: a Kuznetsov-Taylor model and Bell model, that belongs to a general family of tumor-immune stochastic systems. We have determined the equilibrium points and we have calculated the Lyapunov exponents. A computable algorithm is presented in Annexe A1. These exponents help us to decide whether the stochastic model is stable or not. We have also proved stochastic stability by constructing a proper Lyapunov function, under a well chosen conditions. All our results were also proved using graphical implementation. For numerical simulations we have used the second order Euler scheme pre-

sented in detail in Annexe A2 and the implementation of this algorithm was done in Maple 12.

In a similar way can be studied other models that derive from model given by (10). The model given by the SDE (12) allows the control of the system given by the ODE (1), with a stochastic process.

## Annexe

### A1 Lyapunov exponents and stability in stochastic 2-dimensional structures.

#### Lyapunov exponent method

The behavior of a deterministic dynamical system which is disturbed by noise may be modeled by a stochastic differential equation (SDE). In many practical situations, perturbations are generated by wind, rough surfaces or turbulent layers are expressed in terms of white noise, modeled by Brownian motion. The stochastic stability has been introduced in [13] and is characterized by the negativeness of Lyapunov exponents. But it is not possible to determine this exponents explicitly. Many numerical approaches have been proposed, which generally used simulations of stochastic trajectories.

Let  $(\Omega, \mathcal{F}, \mathcal{P})$  a probability space. It is assumed that the  $\sigma$ -algebra  $(\mathcal{F}_t)_{t \geq 0}$  such that

$$\mathcal{F}_s \subset \mathcal{F}_t \subset \mathcal{F}, \forall s \leq t, s, t \in I,$$

where  $I = [0, T]$ ,  $T \in (0, \infty)$ .

Let  $\{x(t, \omega) = (x_1(t), x_2(t))\}_{t \geq 0}$  be a stochastic process, solution of the system of Itô differential equations, formally written as

$$dx_i(t, \omega) = f_i(x(t, \omega))dt + g_i(x(t, \omega))dW(t, \omega), i = 1, 2, \quad (20)$$

with initial condition  $x(0) = x_0$  is interpreted in the sense that

$$x_i(t, \omega) = x_{i0}(t, \omega) + \int_0^t f_i(x(s, \omega))ds + \int_0^t g_i(x(s, \omega))dW(s, \omega), i = 1, 2, \quad (21)$$

for almost all  $\omega \in \Omega$  and for each  $t > 0$ , where  $f_i(x)$  is a drift function,  $g_i(x)$  is a diffusion function,  $\int_0^t f_i(x(s))ds$ ,  $i = 1, 2$  is a Riemann integral and  $\int_0^t g_i(x(s))dW(s)$ ,  $i = 1, 2$  is an Itô integral. It is assumed that  $f_i$  and  $g_i$ ,  $i = 1, 2$  satisfy the conditions of existence of solutions for this SDE with initial conditions  $x(0) = a_0 \in \mathbb{R}^n$ .

Let  $x_0 = (x_{01}, x_{02}) \in \mathbb{R}^2$  be a solution of the system

$$f_i(x_0) = 0, \quad i = 1, 2. \quad (22)$$

The functions  $g_i$  are chosen such that

$$g_i(x_0) = 0, \quad i = 1, 2.$$

In the following, we will consider

$$g_i(x) = \sum_{j=1}^2 b_{ij}(x_j - x_{j0}), \quad i = 1, 2, \quad (23)$$

where  $b_{ij} \in \mathbb{R}$ ,  $i, j = 1, 2$ .

The linearized of the system (21) in  $x_0$  is given by

$$du(t) = Au(t)dt + Bu(t)dW(t), \quad (24)$$

where

$$u(t) = \begin{bmatrix} u_1(t) \\ u_2(t) \end{bmatrix}, \quad A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}, \quad B = \begin{bmatrix} b_{11} & b_{12} \\ b_{21} & b_{22} \end{bmatrix} \quad (25)$$

$$a_{ij} = \left. \frac{\partial f_i}{\partial x_j} \right|_{x=x_0}, \quad b_{ij} = \left. \frac{\partial g_i}{\partial x_j} \right|_{x=x_0}, \quad i, j = 1, 2. \quad (26)$$

The Oseledec multiplicative ergodic theorem [16] asserts the existence of two non-random Lyapunov exponents  $\lambda_2 \leq \lambda_1 = \lambda$ . The top Lyapunov exponent is given by

$$\lambda = \limsup_{t \rightarrow \infty} \frac{1}{t} \log \sqrt{u_1(t)^2 + u_2(t)^2}. \quad (27)$$

By applying the change of coordinates

$$u_1(t) = r(t) \cos \theta(t), \quad u_2(t) = r(t) \sin \theta(t),$$

for (24) and by using the Itô formula for

$$\begin{aligned} h_1(u_1, u_2) &= \frac{1}{2} \log(u_1^2 + u_2^2) = \log(r), \\ h_2(u_1, u_2) &= \arctan\left(\frac{u_2}{u_1}\right) = \theta, \end{aligned}$$

result the stochastic equations written in the integral form.

$$\log\left(\frac{r(t)}{r(0)}\right) = \int_0^t q_1(\theta(s)) + \frac{1}{2}(q_4(\theta(s))^2 - q_2(\theta(s))^2)ds + \int_0^t q_2(\theta(s))dW(s), \quad (28)$$



$$\theta(t) = \theta(0) + \int_0^t (q_3(\theta(s)) - q_2(\theta(s))q_4(\theta(s)))ds + \int_0^t q_4(\theta(s))dW(s), \quad (29)$$

where

$$\begin{aligned} q_1(\theta) &= a_{11} \cos^2 \theta + (a_{12} + a_{21}) \cos \theta \sin \theta + a_{22} \sin^2 \theta, \\ q_2(\theta) &= b_{11} \cos^2 \theta + (b_{12} + b_{21}) \cos \theta \sin \theta + b_{22} \sin^2 \theta, \\ q_3(\theta) &= a_{21} \cos^2 \theta + (a_{22} - a_{11}) \cos \theta \sin \theta - a_{12} \sin^2 \theta, \\ q_4(\theta) &= b_{21} \cos^2 \theta + (b_{22} - b_{11}) \cos \theta \sin \theta - b_{12} \sin^2 \theta. \end{aligned} \quad (30)$$

As the expectation of the Itô stochastic integral is null,

$$E\left(\int_0^t q_2(\theta(s))dW(s)\right) = 0,$$

the Lyapunov exponent is given by

$$\lambda = \lim_{t \rightarrow \infty} \frac{1}{t} \log \left( \frac{r(t)}{r(0)} \right) = \lim_{t \rightarrow \infty} \frac{1}{t} E\left(\int_0^t (q_1(\theta(s)) + \frac{1}{2}(q_4(\theta(s))^2 - q_2(\theta(s))))ds\right).$$

Applying the Oseledec theorem, if  $r(t)$  is ergodic, results that

$$\lambda = \int_0^t (q_1(\theta) + \frac{1}{2}(q_4(\theta)^2 - q_2(\theta)))p(\theta)d\theta, \quad (31)$$

where  $p(\theta)$  is the probability density of the process  $\theta$ .

The probability density is the solution  $p(t, \theta)$  of Fokker-Planck equation associated to equation (29)

$$\frac{\partial p(t, \theta)}{\partial t} + \frac{\partial}{\partial \theta} (q_3(\theta) - q_2(\theta)q_4(\theta)p(t, \theta)) - \frac{1}{2} \frac{\partial^2}{\partial \theta^2} (q_4(\theta)^2 p(t, \theta)) = 0. \quad (32)$$

If  $p(t, \theta) = p(\theta)$ , then the stationary solution of (32) satisfies the first order differential equation

$$(-q_3(\theta) + q_1(\theta)q_4(\theta) + q_2(\theta)q_5(\theta))p(\theta) + \frac{1}{2}q_4(\theta)^2 \dot{p}(\theta) = p_0, \quad (33)$$

where  $\dot{p}(\theta) = \frac{dp}{d\theta}$  and

$$q_5(\theta) = -(b_{12} + b_{21}) \sin(2\theta) - (b_{22} - b_{11}) \cos(2\theta). \quad (34)$$

**Proposition 4.1** *If  $q_4(\theta) \neq 0$ , the solution of equation (33) is given by*

$$p(\theta) = \frac{K}{D(\theta)q_4(\theta)^2} \left(1 + \eta \int_0^\theta D(u)du\right), \quad (35)$$

where  $K$  is determined by the normality condition

$$\int_0^{2\pi} p(\theta) d\theta = 1, \quad (36)$$

and

$$\eta = \frac{D(2\pi) - 1}{\int_0^{2\pi} D(u) du}. \quad (37)$$

The function  $D$  is given by

$$D(\theta) = \exp(-2 \int_0^\theta \frac{q_3(u) - q_2(u)q_4(u) - q_4(u)q_5(u)}{q_4(u)^2} du). \quad (38)$$

□

A numerical solution of the phase distribution could be performed by a simple backward difference scheme. The function  $p(\theta)$  can be determined numerically by using the following algorithm.

Let us consider  $N \in \mathbb{R}_+$ ,  $h = \frac{\pi}{N}$  and

$$\begin{aligned} q_1(i) &= a_{11} \cos^2(ih) + (a_{12} + a_{21}) \cos(ih) \sin(ih) + a_{22} \sin^2(ih), \\ q_2(i) &= b_{11} \cos^2(ih) + (b_{12} + b_{21}) \cos(ih) \sin(ih) + b_{22} \sin^2(ih), \\ q_3(i) &= a_{21} \cos^2(ih) + (a_{22} - a_{11}) \cos(ih) \sin(ih) - a_{22} \sin^2(ih), \\ q_4(i) &= b_{21} \cos^2(ih) + (b_{22} - b_{11}) \cos(ih) \sin(ih) - b_{12} \sin^2(ih), \\ q_5(i) &= -(b_{12} + b_{21}) \sin(2ih) - (b_{22} - b_{11}) \cos(2ih), \quad i = 0, 1, \dots, N. \end{aligned} \quad (39)$$

The sequence  $(p(i))_{i=0, \dots, N}$  is given by

$$p(i) = (p(0) + \frac{q_4(i)^2 p(i-1)}{2h}) F(i),$$

where

$$F(i) = \frac{2h}{2h(-q_3(i) + q_2(i)q_4(i) + q_4(i)q_5(i)) + q_4(i)^2}.$$

The Lyapunov exponent is  $\lambda = \lambda(N)$ , where

$$\lambda(N) = \sum_{i=1}^N (q_1(i) + \frac{1}{2}(q_4(i)^2 - q_2(i)^2)) p(i) h.$$

From (30) and (35) we get the following proposition.

**Proposition 4.2** *If the coefficients of the the matrix  $B$  are given by*

$$b_{11} = \alpha, \quad b_{12} = -\beta, \quad b_{21} = \beta, \quad b_{22} = \alpha,$$

*then the Lyapunov exponent is given by*

$$\lambda = \frac{1}{2}(a_{11} + a_{22} + \beta^2 - \alpha^2) + \frac{1}{2}(a_{11} - a_{22})D_2 + \frac{1}{2}(a_{21} + a_{12})E_2,$$

where

$$D_2 = \int_0^{2\pi} \cos(2\theta)p(\theta)d\theta, \quad E_2 = \int_0^{2\pi} \sin(2\theta)p(\theta)d\theta.$$

$$p(\theta) = Kg(\theta), \quad K = \frac{1}{\int_0^{2\pi} g(\theta)d\theta},$$

$$g(\theta) = \frac{1}{\beta^2} \exp\left(\frac{1}{\beta^2}((a_{21} - a_{12} - \alpha\beta)\theta + \frac{1}{2}(a_{11} - a_{22})\cos(2\theta) + \frac{1}{2}(a_{21} - a_{12})\sin(2\theta))\right).$$

□

### Lyapunov function method

Let us consider the stochastic system of differential equations given by

$$dx_i(t) = f_i(x(t))dt + g_i(x(t))dW_i(t), \quad i = 1, 2, \quad (40)$$

where  $W_1, W_2$  are Wiener processes. Let  $D = (0, \infty) \times \mathbb{R}^2$ , and  $V : D \rightarrow \mathbb{R}$  a continuous function with respect to the first component and of the class  $C^2$  with respect to the other components. Let consider the differential operator given by

$$LV(t, x) = \frac{\partial V(t, x)}{\partial t} + \sum_{i=1}^2 f_i(x) \frac{\partial V(t, x)}{\partial x_i} + \frac{1}{2} \sum_{i=1}^2 \sum_{j=1}^2 g_i(x) g_j(x) \frac{\partial^2 V(t, x)}{\partial x_i \partial x_j}. \quad (41)$$

We suppose that  $x_0 = 0$  is an equilibrium point for (40), that means

$$f_i(0) = g_i(0) = 0, \quad i = 1, 2. \quad (42)$$

The theorem that gives the conditions for stability of the trivial solution  $x_0 = 0$  in terms of Lyapunov function is given in [17].

**Theorem 4.3** *If there is a function  $V : U \rightarrow \mathbb{R}$  and two continuous functions  $u, v : \mathbb{R}_+ \rightarrow \mathbb{R}_+$  and  $k > 0$ , such that for each  $\|x\| < k$ , we have*

$$u(\|x\|) < V(x, t) < v(\|x\|), \quad (43)$$

*then*

- (i) *If  $LV(t, x) \leq 0$ ,  $x \in (0, k)$ , then the solution  $x_0 = 0$  of (40) is stable in probability,*
- (ii) *If there is a continuous function  $c : \mathbb{R}_+ \rightarrow \mathbb{R}_+$  such that*

$$LV(t, x) \leq -c(\|x\|),$$

*then the solution  $x_0 = 0$  of (40) is asymptotically stable.*  $\square$

In general, the functions  $f_i, g_i, i = 1, 2$ , are nonlinear and the above theorem is hard to use. That is why we use the linearization method for the system (40) around the equilibrium point.

The linearized system of stochastic differential equation of (40) is given by

$$\begin{cases} du_1(t) = (a_{11}u_1(t) + a_{12}u_2(t))dt + (b_{11}u_1(t) + b_{12}u_2(t))dW_1, \\ du_2(t) = (a_{21}u_1(t) + a_{22}u_2(t))dt + (b_{21}u_1(t) + b_{22}u_2(t))dW_2. \end{cases} \quad (44)$$

We consider  $D = \{(t \geq 0) \times \mathbb{R}^2\}$  and  $V : D \rightarrow \mathbb{R}$  a continuous function with respect to  $t$  and of the class  $C^2$  with respect to the other components. The theorem that gives the condition that the trivial solution of (44) is exponential  $p$ -stable is given in [1].

**Theorem 4.4** *If the function  $V : D \rightarrow \mathbb{R}$  satisfies the inequalities*

$$k_1\|u\|^p \leq V(t, u) \leq k_2\|u\|^p,$$

$$LV(t, u) \leq -k_3\|u\|, \quad k_i > 0, p > 0,$$

*then the trivial solution of (44) is exponentially  $p$ -stable for  $t \geq 0$ .*  $\square$

In concrete problems, the next theorem is used.

**Theorem 4.5** *If the function  $V : D \rightarrow \mathbb{R}$  satisfies*

- (i)  *$LV(u) \leq 0$ , then the trivial solution is stable in probability;*
- (ii)  *$LV(u) \leq -c(\|u\|)$ , where  $c : \mathbb{R}_+ \rightarrow \mathbb{R}_+$  is a continuous function, then the trivial solution is asymptotically stable;*

- (iii)  $LV(u) \leq -q^T Q q$ , where  $Q$  is a symmetric matrix, positive defined, then the trivial solution is stable in mean square value.

□

For (44), the expression of the differential operator  $LV$  is given by

$$\begin{aligned} LV(t, u) = & (a_{11}u_1 + a_{12}u_2) \frac{\partial V(t, u)}{\partial u_1} + (a_{21}u_1 + a_{22}u_2) \frac{\partial V(t, u)}{\partial u_2} \\ & + \frac{1}{2} \left[ (b_{11}u_1 + b_{12}u_2)^2 \frac{\partial^2 V(t, u)}{\partial u_1^2} + (b_{21}u_1 + b_{22}u_2)^2 \frac{\partial^2 V(t, u)}{\partial u_2^2} \right]. \end{aligned}$$

## A2 The Euler scheme.

In general 2-dimensional case, the Euler scheme has the form:

$$x_i(n+1) = x_i(n) + f_i(x(n))h + g_i(x(n))G_i(n), \quad i = 1, 2, \quad (45)$$

with Wiener process increment

$$G_i(n) = W_i((n+1)h) - W_i(nh), \quad n = 0, \dots, N-1, \quad i = 1, 2,$$

and  $x_i(n) = x_i(nh, \text{omega})$ .  $G_i(n)$  are generated using Box-Muller method.

It is shown that the second Euler scheme has the order for weak convergence 1, for sufficiently regular drift and diffusion coefficients.

We assume that  $f_i$  in (45) are sufficiently smooth such that the following schemes are well defined.

The second order Euler scheme is defined by the relations

$$\begin{aligned} x_i(n+1) = & x_i(n) + f_i(x(n))h + g_i(x(n))G_i(n) + g_i(x(n)) \frac{\partial}{\partial x_i(n)} g_i(x(n)) \frac{G_i(n)^2 - h}{2} + \\ & + \left[ f_i(x(n)) \frac{\partial f_i(x(n))}{\partial x_i(n)} + \frac{1}{2} (g_i(x(n)))^2 \frac{\partial^2 f_i(x(n))}{\partial x_i(n) \partial x_i(n)} \right] \frac{h^2}{2} + \left[ g_i(x(n)) \frac{\partial f_i(x(n))}{\partial x_i(n)} \right. \\ & + \left. f_i(x(n)) \frac{\partial g_i(x(n))}{\partial x_i(n)} + \frac{1}{2} (g_i(x(n)))^2 \frac{\partial^2 g_i(x(n))}{\partial x_i(n) \partial x_i(n)} \right] \frac{hG_i(n)}{2}, \quad i = 1, 2, \end{aligned}$$

where we used the random variables  $G_i(n)$ ,  $i = 1, 2$ . In [12], it is shown that these schemes converge weakly with order 2.

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